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09/598,982	06/21/2000	Mark Maffitt	34506.104	6761

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/598,982	MAFFITT ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,34-37,41-45 and 54-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17,18,43-45 and 54-58* is/are allowed.

6)☒ Claim(s) *1-16,19-25,34-37,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-25, 34-37, 41-45 and 54-58 are pending.

Applicant's amendment of claims 1-3, 7-8, 17-18, 20, 22-24, 34, 37, 43-45, 55-56, cancellation of claims 62-63, and submission of a reference by Peng et al. (Eur. J. Biochem. 270, 270-283, 2003), in a communication filed on 1/7/2005 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claim 34 is objected to due to the recitation of "expresses enzymatically..tryptase". For clarity and consistency, it is suggested that the term be amended to recite "expresses an enzymatically..tryptase". Appropriate correction is required.

Drawings

2. Figure 1 is objected to for failing to comply with the sequence rules. The sequences of tryptase β-I and β-II of Figure 1 do not correspond to the sequence identifiers recited (i.e. SEQ ID NO: 6 and 9). SEQ ID NO: 6 and 9 are 249 amino acids long, do not have the first 30 amino acids prior to the mature fragment shown in Figure 1, and also contain 4 amino acids (LEKR) prior to the mature fragment not found in the sequences disclosed in Figure 1. It is suggested that if these sequences have been disclosed in the sequence listing, the corresponding sequence identifiers be used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6, 8-12, 20-25, 34-36 remain rejected and amended claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

5. Claim 1 (claims 2-6, 9-12, 20-25, 34-36 dependent thereon) is indefinite in the recitation of "a proteolytic tryptase having an active site mutation at an amino acid position selected form positions 44, 91, and 194 of the proteolytic tryptase as shown in Fig. 1, (which positions correspond to residues 48, 95, and 198, respectively, of SEQ ID NO: .....)" for the following reasons. As written, it is unclear if the term "as shown in Figure 1" refers to the proteolytic tryptase having the active site mutation, the tryptase containing the positions recited, or both. If the term refers to both, it is suggested that the term be amended to recite "a proteolytic tryptase as shown in Figure 1 having an active site mutation selected from positions 44, 91, and 194...". For examination purposes, the suggested term will be used. Correction is required.

6. Claims 7-8 are indefinite in the recitation of "a proteolytic tryptase having an active site mutation at an amino acid position selected form positions 44, 91, and 194 of the proteolytic tryptase as shown in Fig. 1, (which positions correspond to residues 48, 95, and 198, respectively, of SEQ ID NO: .....)" for the reasons set forth above, and also because one cannot determine how it further limits the claims. The polypeptides of SEQ ID NO: 21, 23, 25, 27, 37, 39, 41 and 43 do not appear to correspond to the proteolytic tryptases of Figure 1 having an active site mutation at the sites recited since they are 249 amino acid long, lack the first 30 amino acids of the proteolytic tryptases shown in Figure 1, and contain 4 amino acids (LEKR) prior to the mature fragment which are not present in the proteolytic tryptases of Figure 1. Therefore, a DNA encoding the polypeptides of SEQ ID NO: 21, 23, 25, 27, 37, 39, 41 and 43 is not a DNA encoding the proteolytic tryptases of Figure 1 with active site mutations at positions 44, 91, or 194. It is suggested that claims 7-8 be amended such that the term "DNA sequence encoding a

proteolytic tryptase having an active site mutation at an amino acid.....(which positions.....39, 41 and 43), and wherein the DNA sequence ..." be replaced with "DNA sequence encoding a proteolytic tryptase having an active site mutation, wherein the DNA sequence encoding the...having an active site mutation is a DNA sequence selected....". For examination purposes, the term will not be given any patentable weight. Correction is required.

7. Claim 20 (claims 21-25 dependent thereon) is indefinite due to the recitation of "method of producing a mutation ..comprising transforming a eukaryotic host cell with an expression construct according to claim 1, wherein the mutation causes the eukaryotic host cell to express enzymatically inactive ..tryptase" because the method, while reciting in the preamble that it is directed to the production of a mutation, contains steps which are those of a method to produce a mutant tryptase which is enzymatically inactive, i.e. that encoded by the DNA construct of claim 1. It is noted that transformation using the DNA construct of claim 1 does not appear to generate the mutation (e.g. homologous recombination) since the preamble of claim 1 indicates that the DNA construct is an expression construct, i.e. one for recombinant expression of the protein of choice. For examination purposes, it will be assumed that the claim is directed to a method for the production of producing an enzymatically inactive proteolytic tryptase comprising transforming a eukaryotic host cell with the expression construct of claim 1. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 13-16, 19, 37, 41-42 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in the Non Final Action mailed on 10/1/2004.

10. Applicants argue that the amendment of claim 1 overcomes the instant rejection since the claim recites a precise location of the relevant mutations within the ultimate protein expressed by the construct. According to Applicants, the genus of expression constructs recited in claim 1 is disclosed verbatim in the application as filed as evidenced by the sequences listed in Figure 1 and the sequence listing. In regard to claims 13-16, 19, 37, 41 and 42, Applicants argue that the Office is reading limitations out of claim 13. Particularly, Applicants submit that claim 13 does not encompass all of the members of the genus of polynucleotides encoding any active/inactive proteolytic tryptase but rather a genus of proteolytic tryptases having an active site mutation as defined in the specification. In regard to claims 41-42, Applicants submit that the constructs recited in claims 41-42 encode tryptases that self-assemble into enzymatically active tetrameric enzymes without any further intervention, and do not encompass all constructs that express any enzymatically active tryptase.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 13-16, 19, 37, 41-42. The Examiner acknowledges the teachings of the specification and the amendments made to claim 1. In regard to claim 13, the Examiner disagrees with Applicant's contention that the claim encompasses a genus of proteolytic tryptases having an active site mutation as defined in the specification. There is no limitation recited in claim 13 which limits the specific mutations in the active site. As such, claim 13 is directed to a DNA construct which comprises a genus of DNAs encoding any proteolytic tryptase having any mutation in the active site. In regard to claim 41, the Examiner disagrees with Applicant's contention that the claims do not encompass all constructs that express any enzymatically active tryptase. Claim 41 is directed to a DNA construct comprising a genus of DNAs encoding any active proteolytic tryptase. Claim 42 is directed to the DNA construct of claim 41

with the added limitation that the proteolytic tryptase is human. There is no limitation in the claims which limit the genus of tryptases to enzymatically active tetrameric enzymes. However, even if such limitation were to be present, the claims would still be directed to a DNA construct comprising a genus of DNAs encoding any active proteolytic tryptase since tryptases are known to be tetrameric enzymes, as evidenced by Applicant's submitted reference (Peng et al.; Summary, first sentence). As previously indicated, the genera of DNAs required in the claimed constructs is extremely large and structurally variable. It is reiterated herein that while the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, only one species within the genus recited has been disclosed. Also, while a sufficient description of a genus of DNAs may be achieved by a recitation of a representative number of polynucleotides defined by their nucleic acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in the instant case, there is no structural feature recited which is representative of all members of the genus of DNAs encoding (a) any proteolytic tryptase, human tryptase, lung tryptase, or skin tryptase having a mutation in the active site, or (b) any active proteolytic tryptase, human tryptase, lung tryptase, or skin tryptase. The genera of DNAs required encompass a structurally diverse group which cannot be adequately described by a few species known in the art or those described in the specification. Thus, one cannot reasonably conclude that the claimed invention is adequately described.

12. Claims 13-16, 19, 37, 41-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (a) a DNA construct comprising polynucleotides encoding the polypeptides of SEQ ID NO: 9, 21, 23, 25, 27, 37, 39, 41, and 43, (b) eukaryotic host cells comprising the DNA construct of (a), and (c) a method of producing the polypeptides of SEQ ID NO: 9, 21, 23, 25, 27, 37, 39, 41, and 43 by cultivating a eukaryotic host cell transformed with the DNA construct of (a),

does not reasonably provide enablement for (1) a DNA construct comprising polynucleotides encoding any active or inactive proteolytic tryptase, skin tryptase, lung tryptase, or human proteolytic tryptase, (2) eukaryotic host cells comprising the DNA constructs of (1), or (3) a method to recombinantly produce any active or inactive proteolytic tryptase, skin tryptase, lung tryptase, or human proteolytic tryptase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in the Non Final Action mailed on 10/1/2004.

13. Applicants argue that claim 1 has been amended to recite the positions or relevant locations for the mutation with reference to both Figure 1 and the Sequence Listing. In regard to claim 13, Applicants submit that the claim does not encompass all of the members of the genus of polynucleotides encoding any active/inactive proteolytic tryptase but rather a genus of proteolytic tryptases having an active site mutation as defined in the specification. Furthermore, Applicants submit that the specification contains an extensive and enabling description of all aspects of the invention of claim 13.

14. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 13-16, 19, 37, 41-42. In regard to claim 13, as indicated above, the scope of the claim encompasses a DNA construct which comprises a genus of DNAs encoding any proteolytic tryptase having any mutation in the active site, in view of the fact that there is no limitation recited in claim 13 which limits the specific mutations in the active site. The Examiner acknowledges the teachings of the specification, however disagrees with Applicant's contention that the invention claimed is enabled by the teachings of the specification. As indicated previously, the genera of DNAs required in the construct is extremely large and the specification fails to disclose the structural elements in those species disclosed in the specification or the art which are required in any proteolytic tryptase, human tryptase, lung tryptase, or skin tryptase as encompassed by the claims. Furthermore, as discussed previously, isolating the required DNAs is not routine experimentation since the art teaches the unpredictability of isolation

species having the desired function based solely on structural homology. Since structure determines function, one of skill in the art would require some knowledge or guidance as to the structural elements required in any polynucleotide encoding the tryptases recited in the claims. It is also reiterated herein that it is unclear as to whether (a) all proteolytic tryptases, skin tryptases, lung tryptases or human tryptases will have the same structural characteristics at the active site as those of the human proteolytic tryptase disclosed in the instant application, and (2) the mutations made to the active site of a single human proteolytic tryptase can be made to any proteolytic tryptase, human proteolytic tryptase or any skin/lung tryptase (from any source) to inactivate them even if the active site's structural characteristics of these tryptases are different from those of the active site of the human proteolytic tryptase disclosed. Testing an infinite number of polynucleotides to determine which ones encode polypeptides with the desired activity, determining the active site of those which have the desired activity, and determine the mutations which would render the polypeptide inactive would constitute undue experimentation. Therefore, in view of the information provided and the unpredictability of the art, one cannot reasonably conclude that the teachings of the specification or the prior art enable the full scope of the claimed invention.

Allowable Subject Matter

15. Claims 17-18, 43-45, 54-58 appear to be allowable over the prior art of record.

16. Claims 1-12, 20-25, 34-36 appear to be allowable over the prior art of record but are rejected under 35 USC 112, second paragraph for the reasons set forth above.

Conclusion

17. Applicant's amendment of claims 1-3, 7-8, 17-18, 20, 22-24, 34, 37, 43-45, 55-56 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE**

FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 16, 2005

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